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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,526	FALLAUX ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/793,170.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-3 8, 9, 12-14, 17, and 18 have been amended; and claims 21-28 have been added by the amendment filed November 11, 2004.

The cross-reference information as stated currently in the first paragraph of the specification is objected because the status of 09/506,548 needs to be updated. The '548 application is now US Pat No. 6,602,706. In addition, there is no exact indication as to what is the relationship between the International patent application PCT/NL96/00244 and US 08/793,170 or any of the mentioned US filed applications. Correction is requested. The status of the 09/506,548 also needs to be updated since the application has been issued as a US patent.

The currently pending US applications, as recited on pages 8-11 of the IDS dated July 11, 2003, have been considered by the examiner.

Claims 1-28 are pending for examination.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims as currently amended could be reasonably construed as embracing a cell or an isolated cell: 1) comprising a first nucleic acid sequence that not only comprises E1A and E1B functionally active genes but also a portion of an adenovirus pIX gene; 2) encoding a first nucleic acid sequence encoding adenovirus E1A and E1B gene products and yet also being able to express a functionally active pIX gene product by a separate construct which is not the same as a recombinant replication defective adenovirus vector; and 3/ expressing a functionally active pIX gene product which does not necessarily recombine with a second nucleic acid encoding a functionally active pIX gene products, wherein the two gene products do not share any sequence homology necessary for recombination. Claims 9 and 18 are included in the rejection because the claims embrace broadly a "derivative" of the deposited cell line, when read in the context of its respective base claim.

A close review of parent applications, this as-filed specification, together with the claims from the patents issued from the parent application, only shows that applicant at the time the invention was made only envisions to claim an adenovirus packaging cell or isolated adenovirus packaging mammalian cell, which lacks a pIX gene, but comprises a nucleic acid sequence encoding adenoviral E1A and E1B gene products (see US Pat No. 5,994,128, and 6,033,908). More specifically, the only written support with respect

to adenovirus packaging cell lines and pIX based subject matter comes from pages 9 and 26, respectively:

After transfection of HER cells with construct PIG.EIB (*see* FIGS. 4A and 4B), seven independent cell lines could be established. These cell lines were designated PER.CI, PER.C3, PER.C4, PER.CS, PER.C6TM, PER.C8, and PER.C9. PER denotes PGK-EI-Retinoblasts. These cell lines express EIA and EIB proteins, are stable (e.g., PER.C6™ for more than 57 passages), and complement El-defective adenovirus vectors. Yields of recombinant adenovirus obtained on PER cells are a little higher than obtained on 293 cells. One of these cell lines (PER.C6™) has been deposited at the ECACC™ under number 96022940;
New adenovirus vectors with extended E1 deletions (deletion nt. 459 - 3510). Those viral vectors lack sequences homologous to E1 sequences in the packaging cell lines. These adenoviral vectors contain p1X promoter sequences and the plx gene, as plX (from its natural promoter sequences) can only be expressed from the vector and not by packaging cells [***emphasis added***] (Matsui c/ al.s 1986, Hoeben and Fallaux, personal communication; Imler c/ al., 1996); .

As construct PEIA.EIB contains Ad5 sequences nt. 459 to nt. 3510, there is a sequence overlap of 183 nt. between EIB sequences in the packaging construct PIG.EIA.EIB and recombinant adenoviruses, such as, for example, IG.Ad.MLP.TK. The overlapping sequences were deleted from the new adenovirus vectors. In addition, noncoding sequences derived from lacZ, which are present in the original constructs, were deleted as well. This was achieved (see FIG. 10) by PCR amplification of the SV40 po1y(A) sequences from PMLP.TK using primers SV40-1 (SEQ ID NO:8) (introduces a BamHI site) and SV40-2 (SEQ ID NO:9) (introduces a BglII site). In addition, Ad5 sequehces present in this construct were amplified from nt. 2496 (Ad5-1 (SEQ ID NO:10), introduces a BglII site) to nt. 2779 (Ad5-2 (SEQ ID NO:11)). Both PCR fragments were digested with BglII and were ligated. The ligation product was PCR amplified using primers SV40-I (SEQ ID NO:8) and Ad5-2 (SEQ ID NO:11). The PCR product obtained was cut with BamHI and AflII and was ligated into PMLP.TK predigested with the same enzymes. The resulting construct, named PMLPI.TK, contains a deletion in adenovirus E1 sequences from nt. 459 to nt. 3510.

As such, the as-filed application only provides written support for claims that are written similarly to that of the issued claims from US Pat No. 5,994,128, and 6,033,908.

Claims 1-11, and 21-24 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass a genus of cells that are characterized as lacking an unspecified nucleic acid sequence from an adenovirus plX gene, and yet comprise adenovirus E1A and E1B gene products. The specification states on pages 2:

> The invention relates to the field of recombinant DNA technology, more in particular to the field of gene therapy. In particular, the invention relates to gene therapy using materials derived from adenovirus, specifically human recombinant adenovirus.

As such, the claims could reasonably be construed as embracing *in vivo* cells, which are used as a master producer of a gene drug that would affect a pharmaceutical effect in an in vivo environment such as a mammal or human subject. The claims as written are not limit *per se* to isolated or cultured adenovirus packaging or producer cell. As a further evidence of this broad scope, the as-filed application on page 14 states that the cells as claimed "are also intended to be used in vivo as a local producer of recombinant adenovirus, for example, for the treatment of solid tumors". This broad scope is further evidenced by the two set of claims are currently pending. While claims 12-20, and 25-28 are claimed specifically as "an isolated cell", claims 1-11 are claimed generically as just "Cell..." *per se.*

However, a close review of the as-filed specification is that the entire disclosure focuses essentially on an isolated adenovirus packaging cell, which comprises an

exogenous nucleic acid sequence encoding adenovirus E1A and E1B proteins, wherein the nucleic acid sequence lacks a pIX gene. More specifically, the as-filed specification teaches on pages 8-9:

> Furthermore we disclose the construction of novel and improved combinations of packaging cell lines and recombinant adenovirus vectors. We provide:
>
> 1) A novel packaging cell line derived from diploid human embryonic retinoblasts ("HER") that harbors nt. 80-5788 of the Ad5 genome. This cell line, named 911, deposited under no. 95062101 at the ECACC.TM., has many characteristics that make it superior to the commonly used 293 cells (Fallaux et al., 1996);
>
> 2) Novel packaging cell lines that express just E1A genes and not E1B genes. Established cell lines (and not human diploid cells of which 293 and 911 cells are derived) are able to express E1A to high levels without undergoing apoptotic cell death, as occurs in human diploid cells that express E1A in the absence of E1B. Such cell lines are able to trans-complement E1B-defective recombinant adenoviruses, because viruses mutated for E1B 21 kDa protein are able to complete viral replication even faster than wild-type adenoviruses (Telling et al., 1994). The constructs are described in detail below and are graphically represented in FIGS. 1-5. The constructs are transfected into the different established cell lines and are selected for high expression of E1A. This is done by operatively linking a selectable marker gene (e.g., NEO gene) directly to the E1B promoter. The E1B promoter is transcriptionally activated by the E1A gene product, and, therefore, resistance to the selective agent (e.g., G418 in the case of NEO is used as the selection marker) results in direct selection for desired expression of the E1A gene;
>
> 3) Packaging constructs that are mutated or deleted for E1B 21 kDa, but just express the 55 kDa protein;
>
> 4) Packaging constructs to be used for generation of complementing packaging cell lines from diploid cells (not exclusively of human origin) without the need for selection with marker genes. These cells are immortalized by expression of E1A. However, in this particular case, expression of E1B is essential to prevent apoptosis induced by E1A proteins.
> Selection of E1 expressing cells is achieved by selection for focus formation (immortalization), as described for 293 cells (Graham et al., 1977) and 911 cells (Fallaux et al., 1996), that are E1-transformed human embryonic kidney ("HEK") cells and human embryonic retinoblasts ("HER"), respectively;

5) After transfection of HER cells with construct pIG.E1B (see FIG. 4), seven independent cell lines could be established. These cell lines were designated PER.C 1, PER.C3, PER.C4, PER.C5, PER.C6.TM., PER.C8, and PER.C9. PER denotes PGK-E1-Retinoblasts. These cell lines express E1A and E1B proteins, are stable (e.g., PER.C6.TM. for more than 57 passages), and complement E1 defective adenovirus vectors. Yields of recombinant adenovirus obtained on PER cells are a little higher than obtained on 293 cells. One of these cell lines (PER.C6.TM.) has been deposited at the ECACC.TM. under number 96022940;

6) New adenovirus vectors with extended E1 deletions (deletion nt. 459-3510). Those viral vectors lack sequences homologous to E1 sequences in said packaging cell lines.
These adenoviral vectors contain pIX promoter sequences and the pIX gene, as pIX (from its natural promoter sequences) can only be expressed from the vector and not by packaging cells (Matsui et al., 1986, Hoeben and Fallaux, personal communication; Imler et al., 1996);

7) E2A expressing packaging cell lines preferably based on either E1A expressing established cell lines or E1A-E1B expressing diploid cells (see under 2-4). E2A expression is either under the control of an inducible promoter or the E2A ts125 mutant is driven by either an inducible or a constitutive promoter.

Along this main feature of the claimed invention, the specification further teaches

on page 15:

The constructs, in particular pIG.E1A.NEO, can be used to transfect established cells, for example, A549 (human bronchial carcinoma), KB (oral carcinoma), MRC-5 (human diploid lung cell line), or GLC cell lines (small cell lung cancer) (de Leij et al., 1985; Postmus et al., 1988) and selected for NEO resistance. Individual colonies of resistant cells are isolated and tested for their capacity to support propagation of E1-deleted recombinant adenovirus, such as IG.Ad.MLPI.TK. When propagation of E1-deleted viruses on E1A containing cells is possible, such cells can be used for the generation and production of E1-deleted recombinant adenovirus. They can also be used for the propagation of E1A deleted/E1B retained recombinant adenovirus.

Established cells can also be co-transfected with pIG.E1A.E1B and pIG.NEO (or another NEO containing expression vector). Clones resistant to G418 are tested for their
ability to support propagation of E1-deleted recombinant adenovirus, such as IG.Ad.MLPI.TK, and used for the generation and production of E1 deleted recombinant adenovirus and will be applied in vivo for local production of

> recombinant virus, as described for the diploid cells (see previous discussion). All cell lines, including transformed diploid cell lines or NEO-resistant established lines, can be used as the basis for the generation of "next generation" packaging cell lines that support propagation of E1-defective recombinant adenoviruses and that also carry deletions in other genes, such as E2A and E4. Moreover, they will provide the basis for the generation of minimal adenovirus vectors as disclosed herein.

Therefore, the main thrust of the invention, as sufficiently described by the as-filed specification, is the concept of making and use of an isolated adenovirus packaging cell comprising an exogenous nucleic acid sequence which expresses just an adenovirus E1A and E1B proteins but not for an adenovirus pIX. In other words, the as-filed specification does not provide sufficient description of a number of representative number of species of cells other than the ones that were isolated and produced as an isolated adenovirus pIX deficient packaging cell, which is transfected by a DNA that expresses just an exogenous adenovirus E1A and E1B. The as-filed specification does not describe a number of species of cells that are simply expressing adenovirus E1A and E1B endogenously, and yet are characterized as *in vivo* producer cells, in which a sufficient amount of recombinant adenovirus gene therapy vectors can be produced so as to generate a sufficient amount of a gene therapy drug, which is not even recited in any of the claims. While isolated packaging cells are conventionally made in a cultured medium so as to propagate a sufficient amount of adenovirus vectors for use in an *in vivo* gene transfer protocol, such is not the same as claiming a cell which is located in a mammalian subject, expressing adenovirus E1A and E1B, and yet have the ability to propagate a sufficient amount of gene therapy drugs for use in a gene therapy treatment. A disclosure of expressions of adenovirus E1A and E1

proteins in cultured or isolated cells being sufficient to complement and propagate recombinant adenovirus vectors *in vitro* is not the same as a description of *in vivo* cells that could generate a sufficient amount of gene therapy vectors and/or DNA drugs that treat a disease or disorder. The presence of adenovirus E1A and E1B *per se* in a cell does not appear to be sufficient to contribute to a gene therapy effect in a mammal, as contemplated by the as-filed specification.

Thus, it is not apparent how one skilled in the art, on the basis of the written description of this instant application, could envision a representative number of cells or isolated cells as claimed generically. Claiming all nucleic acid vectors that achieve a result without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

An isolated adenoviral producer cell that does not produce replication competent adenovirus, said adenoviral producer cell comprising:

> An adenoviral producer cell that does not produce replication competent adenovirus, said adenoviral producer cell comprising:
>
> one or more recombinant nucleic acid molecules having no overlapping sequences with respect to one another which would otherwise allow for homologous recombination leading to replication competent adenovirus in said

adenoviral producer cell, and wherein said adenoviral producer cell comprises a nucleic acid encoding adenoviral E1 and E1B gene products, said nucleic acid lacking a gene coding for functional or active pIX.

The specification does not reasonably provide enablement for the presently pending claims encompassing any other derivatives as embraced and yet being unspecified by the as-filed specification.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possessing of the full scope of the claims for the reasons set forth above, one skilled in the art would not known how to use and make the full scope of the claimed invention so that it would operate as intended without undue experimentation.

Note also that with respect to claims 9 and 18, which read on a derivative the deposited cell line, the as-filed specification only provide sufficient description and a reasonable enablement for a PER.C6 cells, which is an isolated adenovirus packaging cell, which does not express an adenovirus pIX protein, wherein the cell comprises an

exogenous nucleic acid sequence which expresses just an adenovirus E1A and E1B proteins but not for an adenovirus pIX protein, particularly in view of the reasons set forth in the preceding paragraphs.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

To the extent that the currently amended claims embrace an isolated cell comprising a first nucleic acid sequence that not only comprises E1A and E1B functionally active genes but also a gene coding for an adenovirus pIX gene product, wherein the pIX gene does not necessarily recombine with a recombinant adenovirus replication defective vector lacking the pIX gene, the following rejection is applicable.

Claims 1, 3-8, 10, 12, 14-17, 19, 22, 24, 26, and 28 are rejected under 35 USC 102(e) as being anticipated by Imler (US 6133028).

Imler teaches an isolated mammalian or eukaryotic including those of primary or established cell lines such as human and A549 cells, wherein the cells are made as adenovirus producer cells, which comprises a first nucleic acid sequence that not only comprises E1A and E1B functionally active genes but also a gene coding for an adenovirus pIX gene product, wherein the pIX gene does not necessarily recombine with a recombinant adenovirus replication defective vector lacking the pIX gene. More specifically, Imler teaches the followings:

With respect to the make and use of an adenovirus (replication defective) vector which lacks the pIX gene, Imler teaches:

Thus, the subject of the present invention is an adenoviral vector which is defective for replication, capable of being encapsidated in a complementation cell, which is derived from the genome of an adenovirus comprising, from 5' to 3', a 5' ITR, an encapsidation region; an E1A region, an E1B region, an E2 region, an E3 region, an E4 region and a 3' ITR, by deletion of:

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(i) all or part of the E1A region and the whole of the portion of the E1B region coding for the early proteins; or

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(ii) all or part of the E1A region and all or part of at least one region selected from E2 and E4 regions; or

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(iii) all or part of the E1A region and a portion of the encapsidation region.

An adenoviral vector according to the invention is defective for replication, but capable of being replicated and encapsidated in a complementation cell which provides it in trans with the product(s) for which it is defective so as to generate an adenoviral particle (also termed defective adenovirus) which is incapable of autonomous replication in a host cell but nevertheless infectious, since it has the capacity to deliver the vector to a host cell.

Most particular preference is given to an adenoviral vector according to the invention derived from the genome of a human adenovirus type 5 by deletion of:

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(i) the whole of the portion coding for the early proteins of the E1B region and extending from nucleotide 1634 and ending at nucleotide 4047; and/or

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(ii) the E4 region extending from nucleotides 32800 to 35826; and/or

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(iii) the portion of the E3 region extending from nucleotides 27871 to 30748; and/or

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(iv) the portion of the encapsidation region:

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ranging from nucleotide 270 to nucleotide 346, or

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ranging from nucleotide 184 to nucleotide 273, or

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ranging from nucleotide 287 to nucleotide 358.

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Preferably an adenoviral vector according to the invention is derived from the genome of a wild-type or natural adenovirus by deletion of at least 18% of the said genome, of at least 22%, of at least 25%, of at least 30%, of at least 40%, of at least 50%, of at least 60%, of at least 70%, of at least 80%, of at least 90% or alternatively of at least 95%, and in particular of 98.5%.

With respect to the make and use of a cell line (primary, established human and A549 cells) that comprises a first nucleic acid sequence which encodes adenovirus E1A and E1B, and a portion or the full sequence of the pIX gene, Imler teaches:

> A complementation line according to the invention may be derived either from an immortalized cell line capable of dividing indefinitely, or from a primary line. In accordance with the objectives pursued by the present invention, a complementation line according to the invention is useful for the encapsidation of any defective adenoviral vector, and especially a defective adenoviral vector according to the invention. Thus, when the term "defective adenoviral vector" is used below, it should be understood to refer to any defective vector, of the prior art or of the present invention.
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>
> "Complementation element" is understood to mean a nucleic acid comprising at least the portion of the adenoviral genome in use in the context of the present invention. It can be inserted into a vector, for example of the plasmid or viral type, for example a retroviral or adenoviral vector or one derived from a poxvirus. The case where it is integrated in the genome of a complementation line according to the invention will nevertheless be preferred. The methods for introducing a vector or a nucleic acid into a cell line, and possibly of integrating it in the genome of a cell, constitute conventional techniques well known to a person skilled in the art, as do the vectors which are usable for such purposes. The complementation element may be introduced into a complementation line according to the invention, beforehand or concomitantly with a defective adenoviral vector.
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> According to a specific embodiment, a complementation line according to the invention is intended to complement in trans a defective adenoviral vector for the E1 function. Such a line has the advantage of decreasing the risks of recombination since, contrary to the conventional line 293, it lacks the 5' ITR present in the vectors.
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> In the context of the present invention, a complementation line according to the invention can comprise all or part of the E1A region of the genome of an adenovirus and:
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>
> (i) all or part of at least one region of the adenoviral genome selected from the E1B, E2 and E4 regions, or
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> 82
>
> (ii) all or part of at least two of the E1B, E2 and E4 regions of said genome, or
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> 83
>
> (iii) all or part of the E1B, E2 and E4 regions of said genome.
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> 84
>
> In the context of the invention, said regions may be placed if necessary under the control of suitable elements permitting their expression, but it is preferable to place them under the control of their own promoter, which is inducible by the protein which transactivates transcription encoded by the E1A region.
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> As a guide, a complementation line according to the variant (ii) comprising the E1A, E1B and E4 regions is intended for the preparation of an adenovirus which is defective for the E1 and E4 regions and from which all or part of the corresponding regions has been deleted.

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According to an absolutely preferred embodiment, a complementation line according to the invention is derived from a cell line which is acceptable from a pharmaceutical standpoint. "Cell line which is acceptable from a pharmaceutical standpoint" is understood to mean a cell line which is characterized (whose origin and history are known) and/or which has already been used for the large-scale production of products intended for human use (assembly of batches for advanced clinical trials or of batches intended for sale). Such lines are available from bodies such as the ATCC. In this connection, there may be mentioned the Vero African Green monkey kidney and BHK golden or Syrian hamster kidney lines, the A549 human line derived from a lung carcinoma, and the MRC5 human pulmonary, WI 58 human pulmonary and CHO Chinese hamster ovary lines.

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Alternatively a complementation line according to the invention can be derived from primary cells, and in particular from retinal cells taken from a human embryo.

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The invention also relates to a method for preparing an adenoviral particle according to the invention, according to which:

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an adenoviral vector according to the invention is introduced into a complementation line capable of complementing in trans said vector, so as to obtain a transfected complementation line,

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said complementation line is cultured according to suitable conditions for permitting the production of said adenoviral particle, and

With respect to the teaching of an E1A independent based promoter, Imler teaches:

the Ad2 E2A promoter (nucleotides 27341 to 27030) (in pTG6558),

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the Ad2 E2A promoter from which the sequences lying between nucleotides 27163 and 27182 have been deleted (for pTG6557). Such a mutation enables the baseline level of the E2A promoter to be decreased without affecting the inducibility by the trans-activating protein encoded by E1A.

As such, the Imler reference anticipates the claimed invention as broadly claimed.

Claims 1, 10, 11, 12, 19, and 20 are rejected under 35 USC 103(a) as being unpatentable over Imler taken with Wilson (US 5652224).

TO the extent that Imler does not teach the make and use of an E2A gene produce that includes a t125 temperature sensitive mutation, such is routinely made in the prior art for propagating replication defective adenovirus vectors, as evidenced by Wilson. More specifically, Wilson teaches:

22

> Adenovirus vectors useful in this invention include recombinant, defective adenoviruses optionally bearing other mutations, e.g., temperature sensitive mutations, deletions and hybrid vectors formed by adenovirus/adeno-associated virus sequences. Suitable vectors are described in the published literature [see, for example, Kozarsky I and II, cited above, and references cited therein, U.S. Pat. No. 5,240,846 and the copending applications incorporated herein by reference below.

Thus, it would have been obvious for one of ordinary skill in the art as a matter of enhancing the control and induction or propagation of only replication defective adenovirus vector to includes temperature sensitive mutation in the adenovirus E2A gene product. Such inclusion would ensure that only replication defective adenovirus are propagated in adenovirus producer cells.

Thus, the claimed invention was *prima facie,* obvious.

To the extent that the claims as currently amended contain new matter, and thus, do not enjoy priority from the disclosures of the parent application including those claimed as foreign priority application, and that the claims embrace a isolated adenoviral cell line comprising a separate construct encoding an adenovirus pIX gene product, which is not necessarily the same as replication defective adenovirus vector intended for propagation, the following rejection is applicable.

Claims 1-8, 10, 12-17, 19, 21-28 are rejected under 35 USC 103(a) as being unpatentable over Imler taken with Graham (US Pat No. 6,566,128).

Imler is applied here as indicated above. To the extent that Imler does not teach the make and use of a separate helper construct, which solely expresses an adenovirus pIX gene product, as an alternative for propagating only replication defective adenovirus vectors, such is taught in Graham. More specifically, Graham teaches:

> In accordance with the present invention, helper viruses having genomes of a size greater than the upper limit for packaging in a pIX-defective virion are provided. One embodiment of the present invention is the construction of a helper virus from two vectors. Preferably, the first vector includes a circularized, modified human adenovirus type 5 (Ad5) genome that is deleted for, or contains mutations in, the DNA sequence encoding pIX. This first vector is combined with a second vector containing overlapping viral DNA sequences to generate infectious Ad5, known as a helper virus having a modified pIX, and a genome size greater than the upper limit for packaging in a pIX-defective virion. Alternatively, the size of the helper virus can be increased by the insertion of additional DNA sequences into the adenoviral genome, known as "stuffer" DNA. Bacterial plasmids are preferred vectors for obtaining the helper virus. However, other vectors may be employed to construct the helper virus, such as, for example, yeast plasmids.
>
> Although not able to produce adequate proteins, particularly pIX, to permit its own packaging, the helper virus described herein, is able to produce all of the functions required for the packaging of a helper-dependent viral vector having a genome of appropriately reduced size (i.e., less than about 35 kb) and lacking substantial portions of the viral genome so that the helper-dependent vector DNA can be packaged in pIX-defective virions. Such helper virus and helper-dependent vector DNA may replicate when coinfected into appropriate host cells, but only the helper-dependent vector DNA can be packaged. Optionally, certain regions of the vectors and resulting viruses may be deleted, such as sequences in the Ad E1 or E3 regions that can be omitted from the viral genome without preventing the viral genome from replicating in such cells as may be permissive for replication of said genome in the form of infectious virus.
>
> A fourth embodiment of the invention, provides a mammalian cell line, such as a human cell line that expresses the Ad pIX protein. Alternatively, pIX may be provided by another source, such as a bacterial plasmid or Ad derived vector, that expresses the pIX protein in suitable cells.
>
> The fourth embodiment of the invention, a cell line that supports the replication of the viral components of the invention, that expresses the Ad pIX, and that can be transfected with plasmids described in the previous examples has also been developed. Preferably, the cell line is a human cell line; however, other cell lines are also suitable such as Syrian hamster, mouse, bovine, porcine, or canine cells. These examples are not meant to be limiting as cells derived from other species are also suitable for use with the present invention. A 531 bp fragment of Ad5

> DNA containing the pIX gene was placed under the regulation of an inducible metallothionein promoter or under the control of the human cytomegalovirus immediate early gene promoter and the Simian virus 40 polyadenylation sequence, transfected into 293 cells, and several clones that stably express pIX were identified (Krougliak and Graham 1995, Hum Gene Ther. 6:1575-1586). Cell lines VK2-20, VK4-24 and VK10-9 are capable of complementing a pIX-deficient Ad, and viral titers are similar to that of wild-type virus.

Thus, it would have been obvious for one of ordinary skill in the art to modify the teaching of Imler by constructing a separate helper construct that expresses only an adenovirus pIX gene product in any of the isolated cell of Imler. One of ordinary skill in the art would have been motivated to incorporate the teaching of Graham in the making and use of an isolated adenoviral producer cell of Imler because by having a separate helper construct expressing an adenovirus pIX gene product in an adenovirus producer cell that is employed to propagate adenovirus replication defective vectors, wherein both of the cells and vectors lack the pIX gene, one of ordinary skill in the art, according to the teaching of Graham, would ensure that only the helper-dependent replication defective adenovirus can be packaged and propagated or produced.

Thus, the claimed invention was *prima facie* obvious.

Claims 1, 10, 11, 12, 19, and 20 are rejected under 35 USC 103(a) as being unpatentable over Imler taken with Graham (US Pat No. 6,566,128), and further in view of Wilson (US 5652224).

TO the extent that Imler taken with Graham does not teach the make and use of an E2A gene produce that includes a t125 temperature sensitive mutation, such is routinely made in the prior art for propagating replication defective adenovirus vectors, as evidenced by Wilson. More specifically, Wilson teaches:

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> Adenovirus vectors useful in this invention include recombinant, defective adenoviruses optionally bearing other mutations, e.g., temperature sensitive mutations, deletions and hybrid vectors formed by adenovirus/adeno-associated virus sequences. Suitable vectors are described in the published literature [see, for example, Kozarsky I and II, cited above, and references cited therein, U.S. Pat. No. 5,240,846 and the copending applications incorporated herein by reference below.

Thus, it would have been obvious for one of ordinary skill in the art as a matter of enhancing the control and induction or propagation of only replication defective adenovirus vector to includes temperature sensitive mutation in the adenovirus E2A gene product. Such inclusion would ensure that only replication defective adenovirus are propagated in adenovirus producer cells.

Thus, the claimed invention was *prima facie,* obvious.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over any of claims 1-20 of US Pat No. 5,994,128, claims 1-14 of US Pat No. 6,033,908, claims 1-5 of US Pat No. 6,265,212, claims 1-14 of US Pat 6,306,652, or claims 1-12 of US Pat No. 6,692,966.

The claims are obvious variants because all set of claims encompass the make and use of:

A packaging cell for production of replication defective adenovirus vectors comprising a packaging construct comprising nucleotides 459-3510 of a human adenovirus 5 genome wherein said cell lacks an adenovirus gene coding for functionally active pIX gene products, and wherein said cell comprises nucleic acid sequences coding for functionally active E1A and E1B gene products under the control of a promoter.

Thus, the patent claims and the application claims are obvious variant of one another.

Claims 1-28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over any of claims 26-34 of US Application 10/125,751, and claims 21, 9, and 10 of US Application No. 10/219,414.

The claims are obvious variants because all set of claims encompass the make and use of:

A packaging cell for production of replication defective adenovirus vectors comprising a packaging construct comprising nucleotides 459-3510 of a human

adenovirus 5 genome, wherein said construct lacks an adenovirus gene coding for functionally active plX gene products, and wherein said construct comprises nucleic acid sequences coding for functionally active E1A and E1B gene products under the control of a promoter.

Thus, the patent claims and the application claims are obvious variant of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

DAVE T. NGUYEN
PRIMARY EXAMINER

Dave Nguyen
Primary Examiner
Art Unit: 1632